REMARKS

Applicants appreciate the examiner's statement that claims 162 and 261 are in condition in allowance. Claims 166, 264, and 269 were amended to further clarify the invention. Applicants also note that the examiner inexplicably has withdrawn the allowance of claims 161, 162, 261, 262, 264, 265, and 269 after noting that the claims were in condition of allowance in the Office Action dated October 8, 2004. Claims 161-162, 166, 261-262, 264-265, and 269 are pending in this application for the Examiner's review and consideration.

Claim 166 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. patent No. 5,891,891 to E. Benincasa ("the '891 patent") for the reasons set forth at page 2 of the Office Action.

To anticipate a claim, a single reference must disclose the claimed invention with sufficient clarity to prove its existence in the prior art, and must disclose every element of the challenged claim. *Motorola Inc. v. Interdigital Technology Corp.*, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997); *PPG Industries Inc. v. Guardian Industries Corp.*, 37 U.S.P.Q.2d 1618, 1624 (Fed. Cir. 1996). Absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible Inc.*, 231 U.S.P.Q 160 (Fed. Cir. 1986). Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989).

The Office Action alleges that "[t]he method of using Zolpidem hemitartrate form D for treating insomnia is anticipated by the prior art method of treating insomnia with Zolpidem hemitartrate since the in vivo physiological situation (which is mostly aqueous), the hydrate or hemiethanolate crystalline form of the zolpidem hemitartrate form D having a certain X-ray diffraction pattern no longer exist and would become identical to the Zolpidem hemitartrate of Bennicasa in its use for treating insomnia." Claim 166 recites a method for treating a patient suffering from insomnia by administering a pharmaceutical composition having a therapeutically effective amount of the zolpidem hemitartrate of claim 161. Claim 161 recites zolpidem hemitartrate Form D characterized by a particular PXRD.

The '891 patent discloses the treatment of Parkinson's disease, parkinsonian syndrome, obsessive-compulsive-disorder, and frontal and subcortical dementias. (The '891 patent, col. 1, ll. 9-15). Patients who responded favorably to zolpidem

showed improvement in rigidity, akinesia and bradykinesia, resulting in positive effects on posture and gait. (*Id.* at col. 7, ll. 14-18).

It is black letter law that to anticipate a claim, a reference must teach each and every element of the claim. The '891 patent clearly fails to meet this legal requirement, because the '891 patent does not teach zolpidem hemitartrate Form D. Claim 166 recites a method of treating a patient suffering from insomnia by administration of zolpidem hemitartrate Form D. Because the '891 patent does not teach zolpidem hemitartrate Form D, it cannot anticipate a claim for treating a patient suffering from insomnia with a pharmaceutical formulation of zolpidem hemitartrate Form D.

To remedy this deficiency, the Office Action modifies the claim. In part, the Office Action reads recitations out of the claim while simultaneously adding new limitations to the claim. The Office Action reads out of the claim the dependency on claim 161, thus, ignoring (reading out) that the pharmaceutical formulation comprises zolpidem hemitartrate Form D. Yet this altered claim interpretation is not enough.

The Office Action adds a temporal limitation. Now, the Office Action requires that zolpidem hemitartrate Form D never cease to exist. That is, even after formulation, absorption, and metabolism, zolpidem hemitartrate Form D must never change. Consequently, after removing a claim limitation and adding a new claim limitation, the Office Action erroneously concludes that the '891 patent anticipates claim 166. This analysis, however, fails to meet the basic premise required for anticipation, *i.e.*, that the identical invention must be shown in as complete detail as is contained in the claim.

Accordingly, for the reasons discussed above, the rejection of claim 166 under 35 U.S.C. § 102 (b) as anticipated by the '891 patent cannot stand and should be withdrawn.

Claims 264-267, 269, and 271-272 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. In particular, the Office Action alleges that there is no antecedent basis for the terms "monohydrate" or "hemiethanolate" in base claim 161. The amendments to the claims now render this rejection moot.

Accordingly, for the reasons discussed above, the rejection of claims 264-265, and 269 under 35 U.S.C. § 112, second paragraph, for being indefinite cannot stand and should be withdrawn.

Claims 161, 166, 262, 264-265, and 269 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious over U.S. patent Nos. 6,281,360 ("the '360 patent") to Ettema in view of 6,242,460 ("the '460 patent") and further in view of H.G. Brittain "Polymorphism in Pharmaceutical Solids," (Marcel Dekker Inc, NY 1999) ("the Britain reference") for the reasons set forth on pages 3-4 of the Office Action. Applicants respectfully traverse.

The consistent criterion for determination of obviousness is whether the prior art would have suggest to one of ordinary skill in the art that claimed subject matter should be carried out and would have a reasonable likelihood of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). As the Examiner is well aware, in order to form a proper basis for a rejection under 35 U.S.C. § 103, the prior art must provide some suggestion, either explicit or implicit, of the combination that allegedly renders a claimed invention obvious. *M.P.E.P.*, § 2142 (June 1998), *see also, Panduit Corp. v. Denisson Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir. 1987).

The Examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Sang Su Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); citing *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The need for specificity is paramount, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. *Id.* The Examiner's conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority. *Id.*

"The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." *In re Baird*, 16 F.3d 380, 382, 28 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994); *citing, In re Jones*, 958 F.2d 347, 350, 21 U.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992) (rejecting Commissioner's

argument that "regardless [] how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it.") Until the claimed compounds were actually isolated and purified, it would have been unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained; what cannot be contemplated or conceived cannot be obvious. *In re Deuel*, 51 F.3d 1552, 1558, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995).

The '360 patent discloses the synthesis of imidazopyridine compounds. The hydrogenolysis techniques of the invention are advantageous in that the introduction of halides and halogenated substances into the reaction mixture is avoided as are the corresponding potential impurities. (The '360 patent col. 7, ll. 41-44). Unlike the prior art processes, the invention does not use a halogen in the reduction of the alpha-hydroxy group. (*Id.* at ll. 31-34). The compounds of formula (1), when isolated or recovered by conventional means are generally at least 98% pure and usually more than 99% pure, **without the need to carry out subsequent purification** or the use of special purification/isolation techniques such as HPLC. (*Id.* at ll. 11-16). For clarity, although filtering and crystallization are both technically purification techniques, the "purification" or "special purification" step that is generally unnecessary in the context of the present invention refers to performing a purification technique after the first recovery or isolation of the compound. (*Id.* at ll. 16-21). The high purity level of the compounds of formula (1) is especially advantageous in that it is attained with the free base as opposed to the salt. (*Id.* at ll. 23-26). Although each step of the synthesis provides good purity, crystallization is one form of purification. (*Id.* at ll. 61-65). However, such is **normally not necessary and it typically only employed for characterization purposes**. (*Id.* at ll. 65-67). (Emphasis added).

The '460 patent discloses solid-phase zolpidem salt forms that exhibit improved physical stability. (The '460 patent, col. 3, ll. 61-62). The invention is generally based on the discovery that by forming zolpidem salts that avoid a large amount of unprotonated zolpidem moieties, a zolpidem salt form can be obtain that exhibits superior physical stability in comparison to the known zolpidem tartrate form. (*Id.* col. 2, l. 63 to col. 2, l. 1). Specifically, the presence of a layer of unprotonated zolpidem and/or the presence of methanol as a solvate should be avoided. (*Id.* at col. 5, ll. 11-13). In trying to prepare zolpidem tartrate by crystallization using a 2:1 molar ratio of zolpidem and tartaric acid, and employing non-methanolic solvents such as ethanol, isopropanol, and acetone, results in no

zolpidem tartrate; instead only zolpidem hydrogentartrate is obtained. (*Id.* at ll. 22-27). A salt having a zolpidem to tartaric acid molar ratio of 1:1 is zolpidem hydrogentartrate (*Id.* at col. 6, ll. 24-26). In non-methanolic solvents, the solvent molecule is probably too large to be included into such an oriented crystalline lattice and thus the crystals of zolpidem tartrate are not formed. (*Id.* at ll. 49-52). The zolpidem hydrogentartrate exists in a crystalline form with characteristics such as a DSC showing a single melting exotherm at around 203 °C to 204 °C. (*Id.* at col. 6, ll. 26-32).

The Brittain reference discloses that most drug substances are obtained as microcrystalline powders, from which it is often difficult to obtain crystallographically adequate crystals. (The Brittain reference, p. 235). During the most common evaluation of drug substances, it is usually sufficient to establish only the polymorphic identity of the solid and to verify that the isolated compound is indeed of the desired structure. *Id.* Since every compound produces its own characteristic powder pattern owing to the unique crystallography of its structure, powder x-ray diffraction is clearly the most powerful and fundamental tool for a specification of the polymorphic identity of an analyte. *Id.* p. 236. The Brittain reference characterized the USP description of compound identification as follows: "[t]he USP general chapter on x-ray diffraction states that identity is established if the scattering angles of the ten strongest reflections obtained for an analyte agree to within ± 0.20 degrees with that of the reference material, and if the relative intensities of these reflections do not vary by more than 20 percent." *Id.*

The Office Action readily admits that neither reference teaches nor suggests the 5 peaks in the X-ray diffraction pattern in the instant claim 161, or the DTG thermogram of instant claim 262. See, Office Action p. 4.

The '360 patent fails to render the present claim obvious, because the '360 patent fails to suggested or disclose zolpidem hemitartrate Form D or the DTG thereof. The '360 reference generally discloses the synthesis of zolpidem, but does not disclose zolpidem hemitartrate Form D. Nor does the '360 patent disclose or suggest that zolpidem hemitartrate may exist in polymorphic form. Moreover, the '360 patent teaches against making any particular zolpidem polymorph by discouraging crystallization. The '360 patent emphasizes the innovative hydrogenation step that removes impurities including hydrogenate impurities, thus discouraging crystallization. In fact, the '360 patent limits crystallization for

characterization purposes only. Hence, with this teaching against crystallization, the skilled artisan would not be motivated to crystallize zolpidem hemitartrate, much less crystallize zolpidem hemitartrate Form D.

To remedy the deficiencies of the '360 patent, the Office Action uses the '460 patent. Like the '360 patent, the '460 patent does not disclose or suggest zolpidem hemitartrate Form D. Contrary to the Office Action's position, the '460 patent fails to disclose or suggest zolpidem hemitartrate monohydrate or ethanolate. The '460 patent discloses zolpidem **hydrochloride** monohydrate or ethanolate, a completely different salt-solvate combination.

Furthermore, the proposed combination of the '460 patent and the '360 patent renders both references unsatisfactory for their intended purpose. Example 6 of the '360 patent combines zolpidem (2 eq.) and tartaric acid (1 eq.) in **methanol**. Methanol is the solvent the '460 patent explicitly discourages from use. Yet the Office Action proposes that the skilled artisan after reading the '460 patent (discouraging the use of methanol) would proceed to use methanol in the combination to obtain a stable zolpidem hemitartrate. This combination is contrary to the '460 patent. Accordingly, the combination renders the '460 patent unsatisfactory for its intended purpose, and thus there is no suggestion or motivation to make the proposed modification.

Also, the combination of the references changes the principle of operation of the patents. The suggested combination would require a substantial reconstruction and redesign of the elements shown in the '460 patent as well as a change in the basic principle under which the '460 patent was design to operate. Basically, without any teaching or suggestion, the skilled artisan must change the solvent used in the '460 patent to methanol to be able to combine the references. However, the '460 patent teaches against this modification.

The Office Action states that the "x-ray diffraction pattern having only 5 peaks with or without the DTG thermogram (which is intrinsic to the compound) as recited in the instant [sic, claim] therefore fails to establish the identity of the polymorphic compound and is indistinguishable from the prior art compound." See, Office Action p. 4. This is unsupported by fact or by law as the Office Action has admitted the facts do not support the proposition. Thus, the statement does not remedy the deficiencies of the prior references, because neither the statement nor the Brittain disclose or

suggest the claimed subject matter. The Office Action readily admits neither the '360 patent nor the '460 patent disclose the 5 peaks within the x-ray diffraction pattern.

Contrary to the Office Action's assertions, a review of the application itself demonstrates that each 5 x-ray diffraction peak pattern distinguishes one polymorph over the another. The combination of XRD peaks of form D at 7.1, 9.5, 14.1, 19.6, 24.5 is unique to this form and can be used to unequivocally distinguish form D from the known forms. For example, the Form A XRD diffractogram contains the peaks at 19.5 and 24.5, but it lacks the other three peaks at 7.1, 9.5, and 14.1. The Form C XRD diffractogram contains the peaks at 7.1, 9.5, 19.6, and 24.5, but the peak at 14.1 is missing. The Form E XRD diffractogram contains the peaks at 14.1, 19.6, and 24.5, but the peaks at 7.1 and 9.5 are missing. The Form G XRD diffractogram contains the peaks at 9.5, and 19.6, but the peaks at 7.1, 14.1, and 24.5 are missing. Form H XRD diffractogram contains the peaks at 7.1 and 9.5 but lacks the peaks at 14.1, 19.6, and 24.5. Finally, the Form I XRD diffractogram contains the peaks at 9.5 and 19.6, 24.5, but lacks the peaks at 7.1 and 14.1. Thus, for each polymorph the 5 peak pattern is unique.

Furthermore, the Office Action reads out of the claim the x-ray diffraction recitation, thus concluding that the polymorph "is indistinguishable from the prior art compound." However, the law requires more. The law states that "[t]he need for specificity is paramount, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed." The law further elaborates that "[t]he Examiner's conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority."

Accordingly, the rejection of claims 161, 166, 262, 264-265, and 269 under 35 U.S.C. § 103(a) as rendered obvious by the '360 patent in view of the '460 patent and further in view of the Brittain reference cannot stand and should be withdrawn.

Claims 161, 166, 262, 264-265, and 269 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious over the '891 patent in view of U.S. patent No. 4,382,938 ("the '938 patent") to Kaplan and Wall, "Pharmaceutical Application of Drug Crystal Studies," ("the Wall reference") and further in view of the Britain reference for the reasons set forth on pages 4-5 of the Office Action. Applicants respectfully traverse.

The '938 patent discloses imidazo [1,2-a]pyridine derivatives, useful in therapy and their preparation. (The '938 patent, col. 1, ll. 6-7). The compounds were tested for activity in the area of cerebral circulation, anticonvulsant activity, and sedative or hypnotic activity. (*Id.* at col. 11).

The Wall reference generally discusses the crystalline configurations of pharmaceutical compounds. Different crystal forms act is if they were different compounds, manifesting differences in melting point, solubility, dissolution rate, density, hardness, and/or chemical stability. The Wall reference, p. 33. A polymorphic drug **may** change its crystal structure upon compression or grinding during the tabletting process or during scale-up procedures using different solvent ratios, and the resulting variation **could** drastically affect the pharmaceutical product's solubility or dissolution rate, and hence, it's bioavailability. *Id.* (emphasis added). Dissolution rates of drugs are determined partly by crystal forms, **some** polymorphs have identical dissolution rates, while others vary to a great extent. *Id.* at p. 37 (emphasis added). Some processing operations such as milling or compression **can** trigger a change in a drugs product's crystal structure. *Id.* at p. 38 (emphasis added). For example, compression studies involving 32 drugs known to exhibit polymorphism revealed that **11** (34% percent) were transformed under compression. *Id.*

As discussed above, the '891 patent fails to disclose or suggest any crystalline form of zolpidem, much less zolpidem hemitartrate Form D. Similarly, the '938 patent fails to disclose or suggest any crystalline form of zolpidem, much less zolpidem hemitartrate Form D. The '938 patent discloses crystallization of 6-chloro-2-(4-chlorophenyl)-imidazo[1,2-a]pyridine-3-acetamide from ethanol. The compound is not zolpidem. Nevertheless, without any pointing to any teaching the Office Action equates the compound to zolpidem. Moreover, there is no disclosure or suggestion that such a crystallization is effective with zolpidem hemitartrate. Without either reference mentioning any crystalline zolpidem form or zolpidem hemitartrate Form D, again the Office Action reads out of claim 161 the x-ray diffraction limitations.

To remedy the deficiencies of the '891 patent and the '938 patent, the Office Action relies upon the Wall reference. This reliance, however, is misplaced, as the Wall reference supports applicants contention that zolpidem hemitartrate Form D polymorph exhibits properties distinct from generic zolpidem hemitartrate. The Office Action generically contends that the properties would be obvious, however, the Office Action fails to set forth any suggestion or motivation for one of skill in the art

to produce zolpidem hemitartrate Form D. The generic statement by the Office Action is merely a "suggestion to try." In other words, one of skill in the art would be motivated to try to make zolpidem hemitartrate Form D from generic zolpidem of the '891 patent or the '938 patent, despite neither patent teaching crystallization. The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989).

Finally, the Office Action states that the "x-ray diffraction pattern having only 5 peaks with or without the DTG thermogram (which is intrinsic to the compound) as recited in the instant [sic, claim] therefore fails to establish the identity of the polymorphic compound and is indistinguishable from the prior art compound." See, Office Action p. 5. As discussed above, this statement does not remedy the deficiencies of the prior references as neither the statement nor the Brittain reference fails to disclose or suggest the claimed subject matter. The Office Action readily admits neither the '891 patent nor the '938 patent disclose the 5 peaks within the x-ray diffraction pattern.

Then as above, the Office Action proceeds to read out of the claim the x-ray diffraction limitation and state that the polymorph "is indistinguishable from the prior art compound." This is unsupported by fact or by law as the Office Action has admitted the facts do not support the proposition. The law states that "[t]he need for specificity is paramount, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed." The law further elaborates that "[t]he Examiner's conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority."

Accordingly, the rejection of claims 161, 166, 262, 264-265, and 269 under 35 U.S.C. § 103(a) as rendered obvious by the '891 patent in view of the '938 patent and the Wall reference, and further in view of the Brittain reference cannot stand and should be withdrawn.

Accordingly, it is believed that claims 161-162, 166, 261-262, 264-265, and 269 are now in condition for allowance, early notice of which would be appreciated.

If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is

believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 11-0600.

Respectfully submitted,

Dated: December 28, 2005

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